Inhibitors of tyrosine phosphatases and apoptosis reprogram lineage-marked differentiated muscle to myogenic progenitor cells.

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Public Summary:
Skeletal muscle is formed from and repairs itself by the proliferative capacity of muscle stem cells, which after embryogenesis are primarily the resident satellite cells. Satellite cells can divide ten to a thousand-fold to produce myoblast progenitors that permanently withdraw from the cell cycle and fuse into multinucleated myofibers in vivo (or myotubes in vitro). This capacity to maintain and repair skeletal muscle occurs throughout adult life and is critical for continuing muscle function. Unfortunately, the regenerative capacity of muscle declines in progressive pathologies such as Duchenne muscular dystrophy. In the very young patient, the ongoing degeneration of muscle is compensated for to some extent by regeneration and growth provided by the muscle stem cells, but by the end of childhood that regeneration is insufficient and disease pathology rapidly progresses. Cellularly, the muscle stem cell pools become exhausted in the attempts to repair genetically defective degenerating tissue, and decrease in both number and proliferative ability. As a result, skeletal muscle becomes replaced by fibrous-adipose tissue with subsequent loss of the person's strength, agility and mobility. Any source of autologous replacement muscle stem cells would be valuable for extending both the regenerative capacity of muscle later in life, and as a source for therapeutic cells. Terminally differentiated muscle fibers could be a tremendous source of cells: one fiber is the product of up to a thousand fused myoblasts. However, de-defferentiation or reprogramming mature multinucleated muscle fibers back to progenitor cells is particularly challenging and, until our work, had never been demonstrated before. In our recent work, we genetically labeled, de-differentiated and reprogrammed primary mouse myotubes back into functional myogenic progenitors by the addition of small bioactive molecules. Unlike current cell and gene therapies, no exogenous cells or genes were introduced. This method used to provide functional muscle stem cells to patients in need.

Scientific Abstract:
Muscle regeneration declines with aging and myopathies, and reprogramming of differentiated muscle cells to their progenitors can serve as a robust source of therapeutic cells. Here, we used the Cre-Lox method to specifically label postmitotic primary multinucleated myotubes and then utilized small molecule inhibitors of tyrosine phosphatases and apoptosis to dedifferentiate these myotubes into proliferating myogenic cells, without gene overexpression. The reprogrammed, fusion competent, muscle precursor cells contributed to muscle regeneration in vitro and in vivo and were unequivocally distinguished from reactivated reserve cells because of the lineage marking method. The small molecule inhibitors downregulated cell cycle inhibitors and chromatin remodeling factors known to promote and maintain the cell fate of myotubes, facilitating cell fate reversal. Our findings enhance understanding of cell-fate determination and create novel therapeutic approaches for improved muscle repair.